Armed Forces College of Medicine

AFCM

Wrap up pharmacology GIT

BY

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Anti-emetics

1. Mention the classification of anti-emetic with examples
2. Mention anti-emetics could be used for ttt of motion sickness
3. Mention antiemetics that have prokinetic effects
4. Mention the mechanism of action of the following:

    a) Apreptiant

    b) Ondansetron

1- H1 (histamine) receptor *blockers* (Antihistaminics):

a- Block H_1-receptor in vomiting center.

b- Effective in all vomiting including Motion sickness.

Long acting Useful in sea sickness.

c- E.g. **Dimenhydrinate, Diphenhydramine, Promethazine, Meclizine & Cyclizine.**

2- Muscarinic receptor *blockers*:

- **Hyoscine** ½ mg ½ hr before the journey po or transdermal patch.

  a- Blocks M-receptors in vomiting center.

  b- Effective in ALL vomiting including Motion sickness.

  Short acting Useful in air sickness

3- D2 (Dopamine) receptor *blockers*: Block D_2-receptor in CTZ.

- **Effective in all vomiting EXCEPT motion sickness.**
- **Include:-Metoclopramide, Domperidone, Phenothiazines, Butyrophenones**

- **Metoclopramide**: Antiemetic acting by:

  - Centrally Blocks D_2-receptor in CTZ.

  - Peripherally Stimulate 5-HT_4 receptors in enteric ganglia Release of A.Ch. Gastric motility Gastric emptying Prokinetic agent. This action is antagonized by atropine.

- **Domperidone***:* antiemetic acting by:

  - Centrally Blocks D_2-receptor in CTZ.

  - Peripherally -Blocking activity Gastric motility Prokinetic agent.

- **Phenothiazines: eg Chlorpromazine** & **Butyrophenones: eg Droperidol** & **Haloperidol**.

  - Block D_2-receptor in CTZ. Also Antipsychotics useful in ttt of schizophrenia

4- 5-HT_3 (Serotonin) Receptors *blockers*:

e.g. **Ondansetron** & **Granisetron**

- Block 5-HT3 receptors in CTZ
- Used orally & IV mainly in vomiting induced by cancer chemotherapy.

5- Neurokinin receptor *blockers*: e.g. Aprepitant

- Neurokinin receptors are recently found in vomiting centre where they are stimulated by
- substance P Vomiting & blocked by Aprepitant Antiemetic Action
- **Aprepitant:** Used orally to prevent vomiting induced by cancer chemotherapy
- Side Effects: Fatigue, Dizziness & Anorexia

6- Glucocorticoids: Dexamethazone Used in vomiting due to cancer chemotherapy.

7- Cannabinoids e.g. **Dronabinol**. Used in vomiting due to cancer chemotherapy.

- Mechanism of action: Inhibit dopamine release
- Side Effects:

1. CNS: Euphoria, uncontrollable laugh, weak mental concentration, impairment of reflexes.
2. CVS: Vasodilatation and increase pulse rate

8- Pyridoxine (Vit B-6): Effective in vomiting of pregnancy.

Prokinetics

1. Mention the mechanism of action of the following drugs:
   a) Metoclopromide
   b) Domperidone
   c) Itopride
2. Mention the side effects of metoclopromide
3. Mention four prokinetic drugs
4. Mention prokinetic drugs which have an anti-emetic effect
5. Which of the following prokinetic can cross BBB and cause extrapyramidal effects:

d) Metoclopromide
e) Domperidone
f) Erythromycin
g) Itopride
h) ondansetron

Prokinetic Agents

Drugs which □ GIT motility e.g. **Metoclopramide, Domperidone, Itopride & Erythromycin.**

A- Metoclopramide (Primperan)

□ **Pharmacodynamics:**

1- Antiemetic: mechanism of action:

A. Central: Blocks D_2-receptors in CTZ

B. Peripheral - Stimulate 5-HT_4 receptors in enteric ganglia □ Release of A.Ch. □ □ Gastric motility □□ Gastric emptying □ Prokinetic agent. *This action is blocked by atropine.*

2- Prokinetic agent □□ Gastric motility & emptying.

□ **Therapeutic Uses**: 10 mg 3-4 times/day Orally, Rectally, IM & IV.

- All vomiting EXCEPT motion sickness.
- Gastric Hypomotility e.g. Diabetic gastroparesis.
- Gastro-Esophageal-Reflux-Disease (GERD, Reflux Esophagitis).
- Hiccup.

□ **Adverse Effects :**

1. Dizziness & nervousness.
2. Extrapyramidal manifestations e.g. Parkinsonism & ataxia.
3. Hyperprolactinemia Galactorrhea in females.
4. Absorption of concomitantly administrated drugs e.g. Paracetamol, BUT NOT Digoxin.

B- **Domperidone** (Motelium)

1- **Similar** to Metoclopramide Dual Anti-Emetic & Prokinetic agent:

A. Central: Block D_2-receptors.
B. Peripheral: Block α-adrenoceptors in stomach Motility Prokinetic agent.

This action is **NOT** antagonized by atropine.

2- **Limited** passage across BBB Rare extrapyramidal manifestations BUT STILL can produce hyperprolactinemia.

C- **Itopride** (Ganaton) & **Mosapride** (Gasmovac)

- ⇧ 5-HT_4 receptors in enteric ganglia ⇧ Release of A.Ch. ⇧⇧ Gastric & Colonic motility ⇧ Prokinetic agent: Used in GERD with Proton Pump Inhibitors

D- **Erythromycin:**

1. Macrolide antibiotic.
2. Stimulates motilin receptors on GIT. Rapid *tolerance* to this effect.

purgatives

1. Mention the classification of purgatives
2. Mention four adverse effects of:
   a. Liquid paraffin
   b. Irritant purgatives
3. Mention the mechanism of action of the following drug:
   a. Linacloptide
   b. Lupiprostone
   c. Nalexegol
   d. Docusate sodium
   e. Magnnesium sulphate

Purgatives = Laxatives

Classification of Purgatives:

I. Physical:

1- Bulk forming e.g. Saline purgatives.

2- Lubricant e.g. Liquid paraffin – glycerin suppositories – Evacuate enemas

3- Surfactant (Surface active agents) e.g. Dioctyl Sodium Sulphosuccinate.

II. Irritant Purgatives:

1- Mild irritant e.g. Castor oil.

2- Moderate irritant e.g. Phenolphthalein

3- Severe irritant (obsolete) e.g.Croton oil(زيت الملوك) , Colocynth (الحنظل) & Jalap Severe irritation & diarrhea Dehydration, ulceration & perforation of G.I.T. Not used in therapy

III. Chloride channel activators:

1- Lubiprostone

2- Linactolide

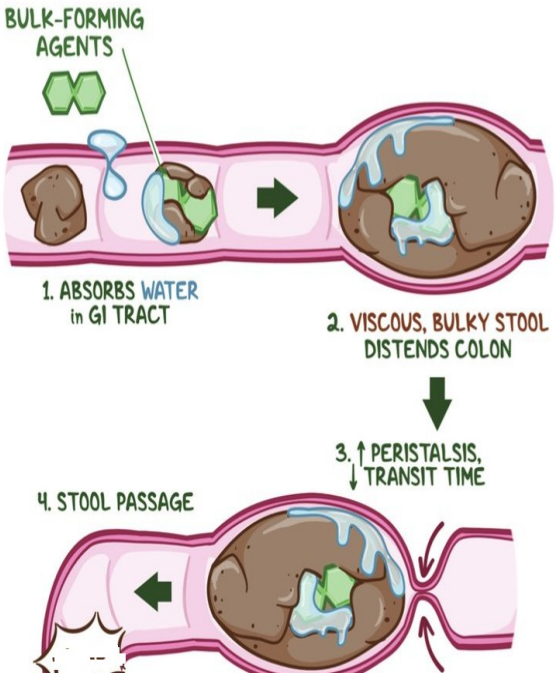
IV. Opioid antagonists:

e.g Naloxegol is a peripherally acting mμ receptor antagonist _

I. Physical Purgatives:

A- Bulk Forming:

- They ↑ bulk of gastric & intestinal contents ⇒ Stretch of wall ⇒ Reflex peristalsis.
- They act on BOTH small & large intestine.
- Onset of action: 1 – 3 hours ⇒ Taken in the Morning.



1- Food containing unabsorbed residues e.g. Vegetables & Bran

Bran *is suitable & safe for chronic constipation in elderly.*

2- Saline Purgatives e.g. Magnesium Sulfate ($MgSO_4$, Epsom's salt)

3- Lactulose:

b- ***Osmotic laxative*** as Not digested & Not absorbed ⇒ Retain water in bowel.

I. Physical Purgatives:

B- Lubricant Purgatives:

○ **Liquid Paraffin = Paraffin Oil:**

1. Synthetic mineral oil Not absorbed orally.
2. Softens & lubricates hard fecal masses & mucosa of **large** intestine.
3. Onset of action: 8-10 hours.
4. Dose: at **night**.
5. Useful in **Chronic Constipation**

I. Physical Purgatives:

B- Lubricant Purgatives:

○ **Liquid Paraffin = Paraffin Oil:**

Disadvantages:

a- Bad consistency, so either add fruit juice or use an emulsion.

b- ↓ Absorption of fat-soluble vitamins (A, D, E & K) ↓

- - ↓ Vitamin D → ↓ Ca^{2+} absorption → ↓ Growth & teething in children.
- - ↓ Vitamin K ↓ Hypoprothrombinemia ↑ Potentiate Oral Anticoagulants.

c- ↓ Absorption of other drugs e.g. Oral Contraceptives.

d- Uncontrolled leakage from anal sphincter ↑

- - Pruritis ani.
- - Anal polyp.
- - Delays healing of anorectal operations e.g. piles & fissures.

I. Physical Purgatives:

C- <u>Surfactants=</u> <u>Surface Active Agents</u>:

○ **<u>Docusate sodium</u> (<u>Dioctyl Sodium Sulfosuccinate</u>)**:

1. Anionic surface active agent → Surfactant = Detergent.
2. Lowers surface tension of hard fecal masses → facilitate penetration of H_2O to stool leading to Wetting & softening of stool.
3. Dose: at night.

N.B.: <u>Stool softeners</u> include Glycerine suppositories, Paraffin oil & Docusate Na.

II. Irritant Purgatives:

- **Mechanism of action:**

Direct stimulation of peristalsis by their irritant effect

- **Disadvantages & Contraindications of Irritant Purgatives:**

1. Colic, diarrhea & dehydration Add small doses of Atropine or Hyoscine.
2. ↓ Absorption of nutrients & drugs.
3. Pelvic congestion:
   A. Menstruation Dysmenorrhea.
   B. Pregnancy Abortion.
4. May be excreted in milk Affect suckling baby.

II. Irritant Purgatives:

A- Mild Irritant Purgatives:

- **Castor Oil:**
  1. Fixed plant oil.
  2. In **small** intestine *Lipase* & ***Bile*** ~~Glycerin +~~ Ricinoleic acid.
  3. Ricinoleic acid Irritates **small** intestine Peristalsis.
  4. Dose : in the **morning**.

II. Irritant Purgatives:

B- Moderate Irritant Purgatives:

1- Anthracine Derivatives:

Examples: **Aloe** (صبر أو صبار), **Cascara** & **Senna** (سنامكي).

a- Colicky pain.

b- Excreted in Milk Diarrhea in suckling baby.

c- Excreted in urine Red discoloration of alkaline urine.

d- pigmentation of mucosa of large intestine

2-Bisacodyl:

- It is prepared as enteric coated tablets to avoid gastric irritation.
- Effective orally (Purgative) & rectally (Suppository)

NB) Sodium Picosulfate is related to Bisacodyl.

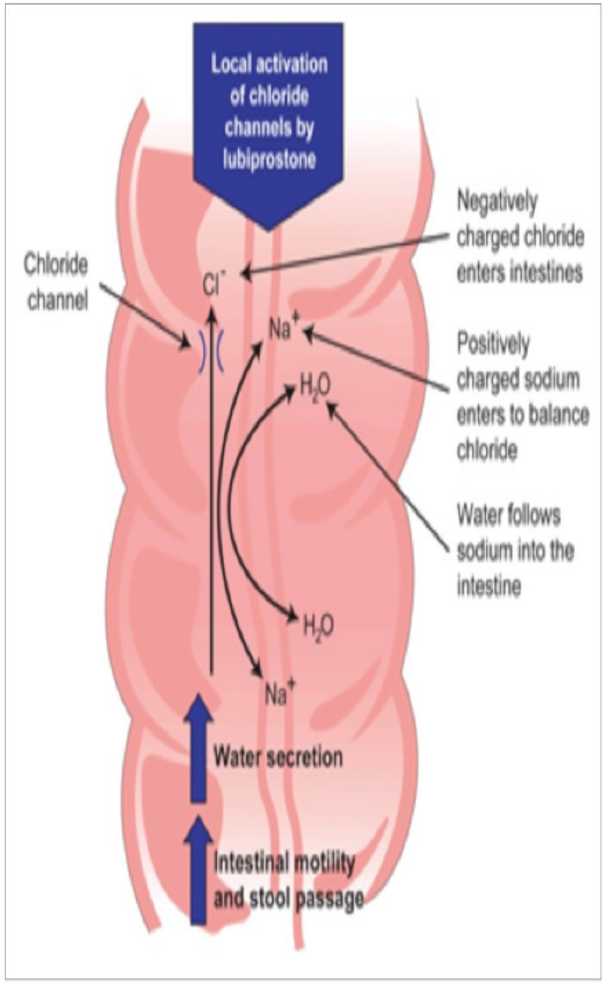
III. Chloride channel activators:

1. Lubiprostone

- **Mechanism of action**
  - It is acts by **activating type 2 chloride channels** to increase fluid secretion in the intestinal lumen.
  - This eases the passage of stool and causes little change in electrolyte balance.

2. Linactolide:

- It stimulates (guanylate cyclase) c GMP, so **indirectly activates** chloride channels



Anti diarrheal drugs

1. Mention two anti-motility drugs with different mechanism of actions
2. Mention two anti-spamodic drugs with different mechanism of actions
3. Cholestyramine is indicated for treatment of …….
4. What is the mechanism of action of **Racecadotril**
5. **Rationalize the use of atropine with moorphine in biliary colics**

II- <u>GIT Protectives</u>: Adsorb toxic substances & provide a coating for the intestine

1. **<u>Adsorbents</u>**: Attraction or holding other materials on its surface

   Kaolin, Bismuth, Chalk & Charcoal.

2. **<u>Absorbents</u>** : Pectin, which is present in rice, carrots, apple.

3. **<u>Astringents</u>** : Causing contraction after topical application

   Tr. Catechu Release tannic acid in intestine & precipitate surface proteins.

III- **Anti-Motility Agents**:

1. **Parasympatholytics:** Atropine & Propantheline. For pain relief of intestinal colic

   Mechanism:

   - Antidiarrheal action: ↓ colonic peristalsis by blocking the response of intestinal smooth muscle to parasympathetic stimulation
   - Antispasmodic action: relieve cramps associated with diarrhea

2. **Opiates**: Diphenoxylate & Loperamide. For symptomatic control of diarrhea

   – Loperamide: Activates u opioid receptors in enteric nervous system with minimal CNS effects.

   – Diphenoxylate: similar to Loperamide but croses blood brain barrier in large doses .

   Mechanism:

   - They act on μ and (delta) receptors in the enteric nervous system leading to ↑ segmenting contractions of the small intestine.

3. **Racecadotril:** is an enkephalinase inhibitor it reduces hypersecretion of water & electrolytes into the intestinal lumen.

IV. Cholestyramine

Mechanism:

- It binds bile acids in the intestine preventing their absorption and decreasing their irritation

Therapeutic uses:

- Diarrhea due to bile salt malabsorption

□ **Treatment of Colic = Antispasmodics:**

1. **Parasympatholytics** e.g. Atropine and its antispasmodic substitutes: e.g. Propantheline
2. **Direct Spasmolytics**:
   - Volatile oils (peppermint), Kheline, papaverine
   - **Mebeverine** □ *Direct spasmolytic* □ Useful in colon spasm.

□ Treatment of Biliary Colic:

1. **Atropine & its substitutes** e.g. Hyoscine butyl bromide
2. **If severe pain**:

– Narcotic analgesics Morphine + Atropine (Never morphine alone) or Meperidine alone. Or Potent Antipyretic analgesics: NSAIDs as diclofenac IM

Irritable Bowel Syndrome

1. Mention drugs used for ttt of IBS with:

a) Constipation

b) Diarrhea

IBS-Antispasmodic

Dicyclomine hydrochloride

Hyoscyamine

Mebeverine hydrochloride

Peppermint oil

mechanism of Action :blocks the action of acetylcholine at parasympathetic sites in secretory glands, smooth muscle, and CNS

NB: Peppermint oil and certain **antispasmodics may** be effective for global symptoms and **abdominal pain.** (ACG guidelines 2020)

IBS-C → Laxatives

- **Polyethylene glycol**
- **Bulk forming laxatives e.g. methyl cellulose**

- **Resistant cases**
- **Serotonin : Selective 5 HT4 receptor agonists e.g. prucalopride-Tegaserod**
- **Local : Linaclotide –lupiprostone**
- **Patients who have not responded to osmotic laxatives and laxatives from the different classes and who have had constipation for 12 months can be treated with Linaclotide.**

IBS-D → Anti-diarrheal drugs:

- Loperamide hydrochloride (an opioid receptor agonist in GIT) is the first line choice for relief of diarrhea.
- The drug **does not pass the blood brain barrier and has neither analgesic properties nor potential for addiction.**

IV. Anti-depressants

A. Low dose of tricyclic antidepressants (e.g amitriptyline or despiramine)

- They decrease the abdominal pain by altering of visceral afferent information.
- They have **anti-muscarinic properties** so they decrease the GIT motility secretions reducing stool frequency and liquidity.

At these doses, these drugs have no effects on mood.

B. A selective serotonin reuptake inhibitor can be given in those who do not respond to a tricyclic anti-depressant.

Examples: escitalopram ,fluoxetine

C. Psychological intervention can be offered to patients who have not relief of IBS symptoms after 12 months of drug treatment.

- Rifaximin
- is a semisynthetic derivative of rifampin and acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase, blocking one of the steps in transcription. The exact mechanism of action for IBS-D is not known, but it is thought to be related to changes in the bacterial content in the gastrointestinal tract and reduction of gas.

•We recommend the use of rifaximin to treat global IBS-D symptoms.

- **Strong recommendation; moderate level of evidence.(ACG 2020)**

MCQs

The following antiemetic drug is useful in treatment of motion sickness

a) Dimenhydrinate
b) Chorpromazine
c) Halopridol
d) Metocloprpmide
e) domperidone

The following purgative interfere with absorption of fat soluble vitamins

a) Liquid paraffin
b) Methyl cellulose
c) Lactulose
d) Magnesium sulphate
e) Docusate sodium

All the following are used in the treatment of diarrhea except

a) Kaolin
b) Neostigmine
c) Loperamide
d) Oral rehydration solution
e) Atropine

Loperamide is

a) Analgsic antipyretic
b) Anti-tussive
c) Anti-emetic
d) Anticonvulsant
e) Anti-diarheal

Drugs useful to control vomiting include the following except

a) Chlorpromazine
b) Domperidone
c) Apomorphine
d) Ondansetron
e) hyoscine

Ondansetron is useful in treatment of

a) Vomiting induced by cancer therapy
b) Motion sickness
c) Vomiting of pregnancy
d) Acute migraine
e) Acute diarrhea

Which of the following is direct spasmolyics

a) Atropine
b) Mebeverine
c) Morphine
d) Aminophylline
e) propantheline

Physical purgatives include which of the following

a) Docusate sodium
b) Bisacodyl
c) Croton oil
d) Castor oil
e) loperamide

A 58 year-old woman presents with diabetic gastroparesis and is prescribed metoclopromide, adrug that act as a

a) B1 antagonist
b) M antagonist
c) Glucocorticoid
d) D2 antagonist
e) 5HT1 antagonist


Best Wishes!